GB99/01777

The Patent Office

PCT/GB99/01777

09/700909

INVESTOR IN PEOPLE

REC'D 30 JUL 1999
WIPO PCT

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed D. Mahoney

Dated 24 June 1999

PRIORITY DOCUMENT

SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Patents Form 1/77

Patents Act 1977
(Rul

THE PATENT OFFICE
D
- 6 JUN 1998
RECEIVED BY

The Patent Office

06 JUN 1998 1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form.)

9
08JUN98 E365923-1 D01631
P01/7700 25.00 -9806

The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

Fee: £25

1. Your reference

39763/JMD

2. Patent application number
(The Patent Office will fill in this part)

9812097.5

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

CeNeS Limited
St. John's Innovation Centre,
Cowley Road,
Cambridge CB4 4WS.

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of incorporation

United Kingdom

4. Title of the invention

Morphine-6-Glucuronide Synthesis

5. Full name, address and postcode in the United Kingdom to which all correspondence relating to this form and translation should be sent

Reddie & Grose
16 Theobalds Road
LONDON
WC1X 8PL

Patents ADP number *(if you know it)*

91001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application *(If you know it)*	Date of filing *(day/month/year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day/month/year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

YES

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document.

	Continuation sheets of this form
Description	6
Claim(s)	2
Abstract	0
Drawing(s)	1 d1

10. If you are also filing any of the following, state how many against each item.

Priority documents	0
Translations of priority documents	0
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	0
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	0
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature: Reddie & Grose

Date: 4 June 1998

12. Name and daytime telephone number of person to contact in the United Kingdom: J M DAVIES 0171-242 0901

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or such direction has been revoked.

Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.*

b) *Write your answers in capital letters using black ink or you may type them.*

c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*

d) *If you have answered 'Yes' Patents Form 7/77 will need to be filed.*

e) *Once you have filled in the form you must remember to sign and date it.*

f) *For details of the fee and ways to pay please contact the Patent Office.*

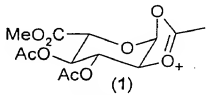
Morphine-6-Glucuronide Synthesis

The invention provides a novel method for synthesising M6G, and intermediates therefor.

In order to synthesise M6G the major problem to overcome is to obtain the glycoside linkage with very high β-selectivity since prior methods produce the α-anomer.

One method for obtaining high β-selectivity is to use trichloroimidate as the leaving group, as shown in WO 93/03051: Figure 1 (Salford Ultrafine Chemicals and Research Limited).

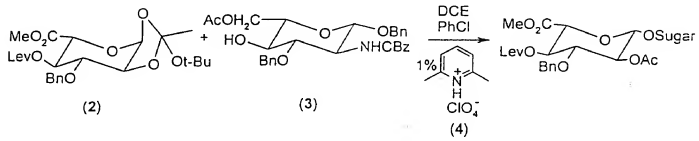
According to the invention, a reaction, which involves the activation of a group on the anomeric position to give the oxonium ion as a reactive intermediate, which also has an acetate group at the C(2) position, proceeds via the cyclic intermediate (1).



(1)

This has an important controlling effect on the stereochemistry on the anomeric site, ensuring that only the β-anomer is obtained in the final product.

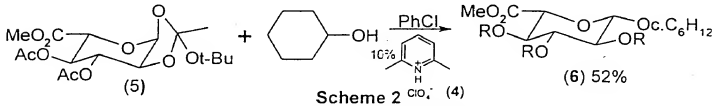
Orthoesters are simple to synthesise from their respective bromides[1]. There is a reacti
reported in the literature[2] between the glucuronate orthoester (2) and the sugar derivative (3) catalysed by lutidinium perchlorate[3] (4) (Scheme 1).



(2) (3) (4)

Scheme 1

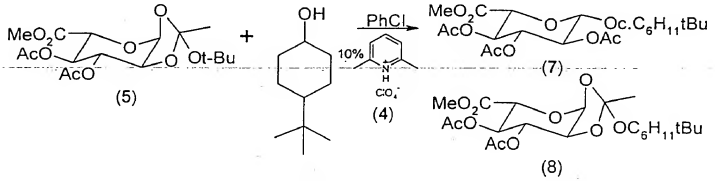
When this reaction was repeated with the t-butyl orthoacetate (**5**) and cyclohexanol (6 equivalents), the desired product (**6**) was isolated in 9% yield. Two other products also suggested that they were the desired product, but with the loss of one acetyl group, isolated in a combined yield of 43% (Scheme 2).



(5) (4) (**6**) 52%

Scheme 2

When 1.2 equivalents of 4-*tert*-butylcyclohexanol was used, the desired compound (**7**) was obtained in 17% yield. Other compounds obtained from the reaction also appeared to contain the desired peaks in the nmr, but after further examination proved to be the product of transorthoesterification (**8**) (Scheme 3).

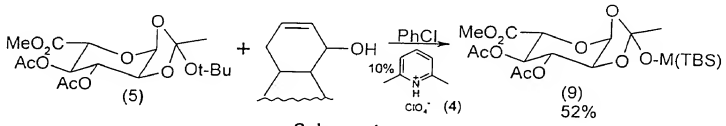


(5) (4) (**7**) (**8**)

Scheme 3

Reaction of orthoester (5) with protected morphine

Initially, 1.2 equivalents of 3-TBS protected morphine and the orthoester (**5**) were dissolved in chlorobenzene and half of the solvent was distilled off before 0.1 equivalents of lutidinium perchlorate (**4**) in chlorobenzene was added. The solvent was continuously distilled off while fresh solvent was added, and after 2.5 h another compound was formed with similar tlc properties to the protected morphine. Workup and chromatography gave a compound which corresponded to trans-orthoesterified material (**9**). None of the desired material was obtained (Scheme 4).



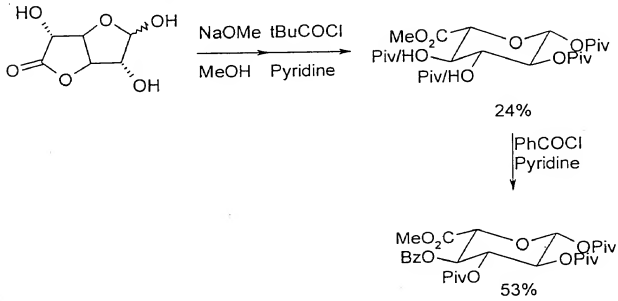
Scheme 4

This product (**9**) was resubmitted to the reaction conditions (0.1 equivalents of lutidinium perchlorate and protected morphine in refluxing chlorobenzene) with no new products formed after 4h. Two further reactions were attempted using two equivalents of orthoester (**5**) and 0.2 equivalents of lutidinium perchlorate and 1 equivalent of orthoester (**5**) and 1.2 equivalents of lutidinium perchlorate, but both gave varying yields of orthoester (**9**).

We have concluded that a different, more bulky, alkyl group was needed on the orthoester to hinder attack there. Initially, the isopropyl group was examined. However, the initial reaction, perisobutyrylation, failed to give a compound which recrystallised from petrol, so the α and β anomers could not be separated. Therefore, attention focussed on the pivaloyl group.

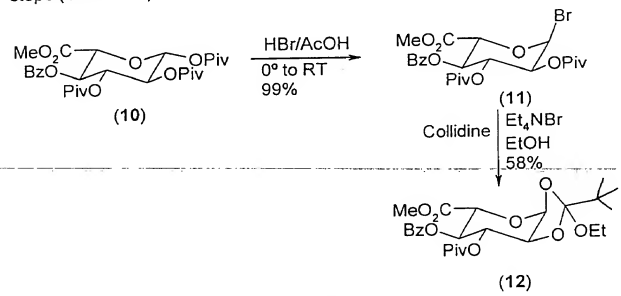
Synthesis of the ethylorthopivalate (12)

Perpivalation turned out to give a mixture of 3 and 4 non-pivalated material, which was benzoylated (Scheme 5).



Scheme 5

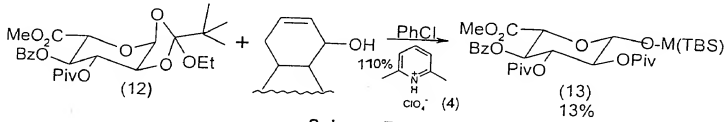
This particular isomer (**10**) was subjected to bromination (HBr/AcOH) and orthoesterification (Et_4NBr, collidine, EtOH) to give the orthoester (**12**) in 57% for 2 steps (Scheme 6).



Scheme 6

Reaction of orthoester (12) with protected morphine

Subjecting the orthoester (**12**) to 1.1 equivalents of both TBS protected morphine and lutidinium perchlorate in distilling chlorobenzene for 2h gave another product close to TBS protected morphine on tlc. Workup and purification by chromatography gave a compound (**13**) which corresponds to protected M6G (with no detectable quantity of α-anomer) from nmr analysis (Scheme 7).



Scheme 7

A final step in the synthesis of M6G is to hydrolyse the protecting groups from this compound.

This could be achieved in a number of known ways, including that of WO 93/03051.

Steps which might improve the above scheme may include:

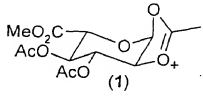
- Carrying out the bromination and subsequent reactions on the C(3) and C(4) non-pivalated material (as these unprotected hydroxyls are relatively unreactive). Heating the perpivalation reaction to reflux gives a moderate yield of fully pivalated material and it may be desirable to optimise this reaction.
- Attempting to couple the morphine to the brominated material by using a suitably hindered amine base such as *N,N*-di-*iso*-propylethylamine (Hönig's Base). This is based on the observation that on forming the orthoester a small amount of material was formed that appeared to represent direct coupling of ethanol to the anomeric position.
- Changing the base used in the orthoester forming reaction from collidine (which boils at 170°C) to a lower boiling point amine. A catalytic amount of DMAP (4-*N,N*-dimethylaminopyridine) may also be used.
- This reaction could also be done successfully with tosic acid (cheaper and less hazardous) rather than the lutidinium perchlorate (4) used.

References

1. For a review of orthoesters and their synthetic applications see N. K. Kochetkov and A. F. Bochkov, *Recent Developments in the Chemistry of Natural Carbon Compounds,* Ed. R. Bognár, V. Bruckner, and Cs. Szántay, Akadémiai Kiadó: Budapest, 1971, vol. 4, p.77-191.
2. H. P. Wessel, L. Labler, and T. B. Tschopp, *Helv. Chim. Acta.*, 1989, **72**, 1268.
3. The use of 2,6-dimethylpyridinium perchlorate (**4**) was first reported by N. K. Kochetkov, A. F. Bochkov, T. A. Sokolovskaya, and V. J. Snyatkova, *Carbohydr. Res.*, 1971, **16**, 17.

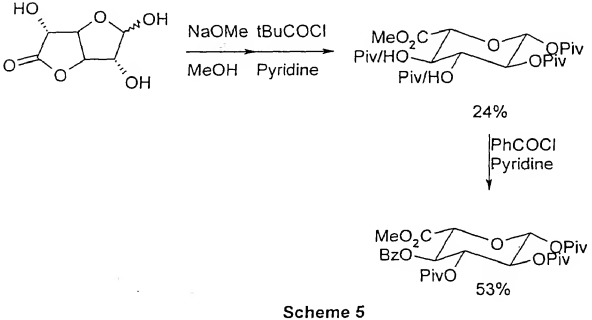
aims

1. A method for the preferential synthesis of the β-anomer of M6G, which involves the activation of a group on the anomeric position to give the oxonium ion as a reactive intermediate, which also has an acetate group at the C(2) position, and which proceeds via the cyclic intermediate (1).



(1)

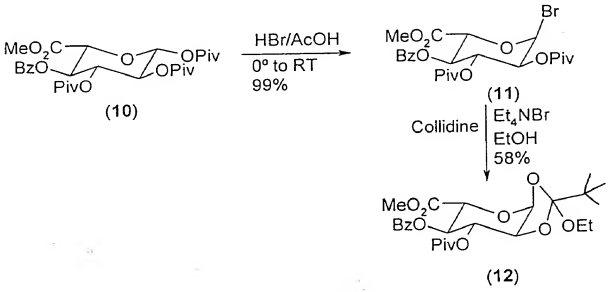
2. Synthesis according to claim 1 which includes the step shown in Scheme 5:



(10)

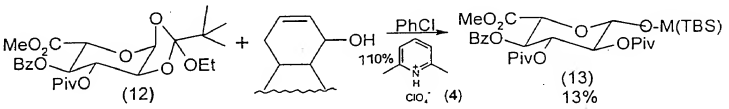
Scheme 5

3. Synthesis according to claim 1 or 2 which includes the step shown in Scheme 6:



Scheme 6

4. Synthesis according to claim 1, 2 or 3 which includes the step shown in scheme 7:



Scheme 7

5. Synthesis according to claim 4 which includes a step to hydrolyse the protecting groups from compound (13).

6. In intermediate compound of formula (1) or a side-group-protected derivative thereof for use in a method of claim 1.

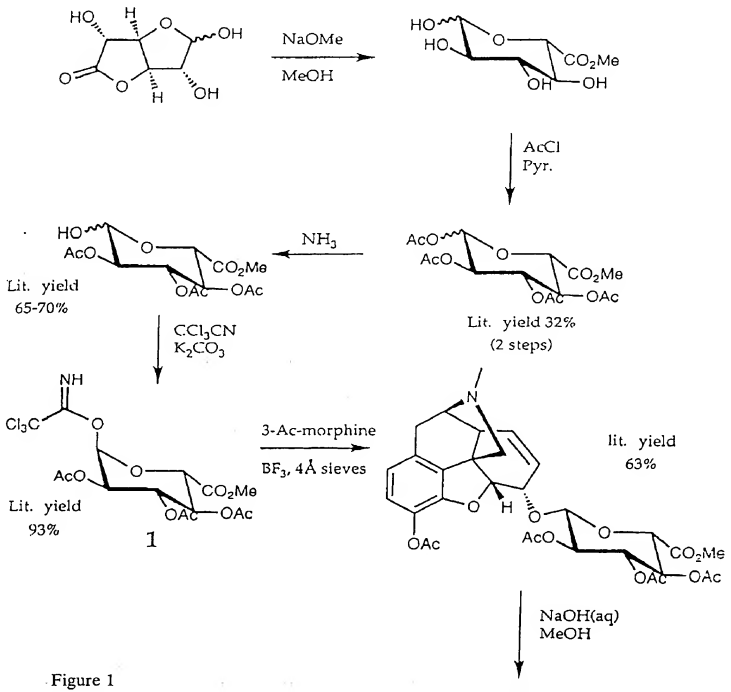


Figure 1

Prior Art